Normal Dermal Ferrochelatase Activity Does Not Protect Human Skin from Protoporphyrin-Induced Photosensitivity

To the Editor:

In the January issue of the Journal, Pawliuk *et al* (2005) report that normal mice transplanted with bone marrow from a mouse model of erythropoietic protoporphyria (EPP), BALB/C-Fech^{m1Pas}, have serum and erythrocyte protoporphyrin concentrations that are as high as those in the photosensitive donors and yet show only minimal photosensitivity and, unlike the donors, do not develop liver damage. Furthermore, skin grafts from normal mice were not photosensitive when implanted onto the backs of protoporphyric mice.

From these fascinating experiments, the authors conclude that "in the presence of normal cellular levels of hepatic and dermal ferrochelatase (FECH), elevated plasma protoporphyrin levels alone are insufficient to generate EPP-associated liver disease and significant photosensitivity" and suggest that their findings may provide new strategies for treatment of EPP.

Can these observations be extended to humans? Clinical observations suggest not. In their discussion, the authors consider one argument against their hypothesis, namely the occasional recurrence of disease in the donor liver after transplantation for protoporphyric liver failure. But they, and the accompanying Editorial (Lim, 2005), overlook another clinical observation that is perhaps more pertinent to their experiments.

The onset of EPP after the age of 40 y is very rare. When it does occur, it is usually associated with myelodysplastic syndrome (MDS) or a related disorder (Lim *et al*, 1992). Recent molecular investigation of such cases has shown that they develop EPP as a direct consequence of expansion in their bone marrows of a clone of hemopoietic cells in which deletion of one *FECH* allele leads to massive overproduction of protoporphyrin (Aplin *et al*, 2001; Goodwin *et al*, 2002). For all other tissues, evidence from analysis of germline DNA (Aplin *et al*, 2001; Goodwin *et al*, 2002), and the observation that EPP disappears after bone marrow transplantation (Lim *et al*, 1992), suggests that FECH activity is likely to be normal, as would be expected given the hematopoietic stem cell origin of MDS.

Abbreviation: EPP, erythropoietic protoporphyria

This experiment of nature in humans closely parallels those described in mice by Pawliuk *et al* (2005). Yet, in spite of their presumed normal dermal and hepatic FECH activities, these patients have severe skin photosensitivity (Lim *et al*, 1992; Aplin *et al*, 2001), and one recently reported case also developed acute protoporphyrin-induced liver damage (Goodwin *et al*, 2002). Thus, in humans, an elevated plasma protoporphyrin concentration does seem to be all that is required to produce severe skin photosensitivity. Restoration of dermal FECH activities to normal may therefore have less promise as a treatment for EPP than the intriguing experiments of Pawliuk *et al* (2005) would suggest.

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See related article on page 580

Skin Ferrochelatase Levels and Photosensitivity

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Can the seemingly intuitive clinical counter-examples provided by Elder rule out the possibility that restoring or enhancing ferrochelatase activity in the skin of human patients with the congenital erythropoietic protoporphyria (EPP) may prevent skin photosensitivity? We think not.

Abbreviation: EPP, erythropoietic protoporphyria